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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/647,561

08/25/2003

Michael David Bentley

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NEKTAR THERAPEUTICS  
201 INDUSTRIAL ROAD  
SAN CARLOS, CA 94070

EXAMINER

HEARD, THOMAS SWEENEY

ART UNIT

PAPER NUMBER

1654

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/647,561	<b>Applicant(s)</b> BENTLEY ET AL.	
	<b>Examiner</b> THOMAS S. HEARD	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-3, 6-19, 23, 24, 26 and 27 is/are pending in the application.
- 4a) Of the above claim(s) 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6-19, 23, 26 and 27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>02/15/2008</u>  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

The Applicants Amendments to the claims received on 2/15/2008 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 10/16/2007 are hereby withdrawn.

Claim(s) 1-3, 6-19, 23, 24, 26 and 27 are pending. Applicants have amended claim(s) 1, 8, 18 and 19. Claims 24 drawn to DPDPE is withdrawn, being drawn to non-elected subject matter. Applicant's elected species is biphalin and is readable upon 1-3, 6-19, 23, 26 and 27. Claims 1-3, 6-19, 23, 26 and 27 are hereby examined on the merits.

#### ***Claim Rejections - 35 USC § 112***

Applicant's amendments to the claims have overcome the rejection of Claims 1-3, 6-19, 23, 24, 26, and 27.

#### ***Claim Rejections - 35 USC § 103***

Applicant's amendments have overcome the rejection of Claims 1-3, 5-19, 21, 23, 26, and 27. Applicants have amended the claims from comprising to consisting, narrowing the scope of the invention such that the prior art does not read on instantly claimed invention. Therefore, the rejection is withdrawn in light of the amendment.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. *Joy Technologies Inc. V. Quigg*, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In *re Hoeschele*, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In *re Clinton*, 188 USPQ 365, 367 (CCPA 1976); In *re Thompson*, 192 USPQ 275, 277 (CCPA 1976).

Claims 1-3, 6-19, 23, 26 and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over

Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," *Crit Rev Ther Drug Carrier Syst.* 1992;9(3-4):249-304;

Wu D, Pardridge WM., "Neuroprotection with noninvasive neurotrophin delivery to the brain," *Proc Natl Acad Sci U S A.* 1999 Jan 5;96(1 ):254-259; and

Sakane et al., "Carboxyl-directed Pegylation of Brain-derived Neurotrophic Factor Markedly Reduces Systemic Clearance with Minimal Loss of Biological Activity," Pharm Res., 14(8):1085-1091 (1997). Wu et al and Sakane et al are of record in Applicant's IDS and Delgado et al is of record in previous office actions

The instantly claimed invention is drawn to a hydrophilic polymer-peptide conjugate consisting of a peptide that is either biphalin (Applicant's elected species) or [D-Pen2, D-Pens] enkephalin (DPDPE) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier

Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al teaches a wide range of benefits of PEGylating a protein which are 1) increased plasma half-life, 2) reduced renal clearance, 3) reduced cellular clearance, 4) reduced proteolysis, 5) reduced immunoclearance, 6) reduced immunogenicity and antigenicity, and 7) increased solubility, among 8) other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins, and that the PEG is determining the property. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000 MW readable upon PEG ranging from 10 to 2000, readable on Claims 3, 6-10, 11-16, 18-19, 26, and 27. Note that in Claim 3 is a negative

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limitation that is readily apparent in the examples of Delgado et al, see Figure 3 for example. The linkage to the Tyrosine as claimed in Claim 19 would be at the N-terminus because the Tyrosine is the N-terminal amino acid and meets the limitation of those Claims 19 as well as Claim 6 and 7. Delgado et al teaches a plurality of different PEG moieties readable upon co-polymers of Claim 8 as well as polyethylenen glycol of Claims 1, 6, 7, 10-, 18, 19, 26, and 27. Delgado et al does not, however, teach the pegylation of the neuropeptide biphalin.

Wu et al teaches a neuropeptide (BDNF) that has been PEGylated (2000 MW) and further chemically modified to include a biotin/OX26Mab composition (diagnostic agent by the Applicant's specification) on the terminus of the PEG for transport across the blood brain barrier (BBB). The neuropeptide (BDNF) had the benefits of PEGylation taught by Delgado et al. Wu et al states that *"there are more than 30 known neurotropic factors and there molecules may prove to be powerful neuropharmaceuticals should they be enabled to undergo transport through the BBB with optimized plasma pharmacokinetic properties"* The optimized properties results from the PEGylation of the peptide and as Delgaso et al taught, Wu confirmed for the neuropeptide BDNF.

Sakane et al teaches the C-terminal pegylation of a neuropeptide (BDNF). Sakane et al teaches that the *"PEG-BDNF is shown to have markedly reduced rates of plasma clearance following carboxy-directed protein pegylation, which results in optimized pharmacokinetic properties,"* in full agreement with Delgato et al supra as well as Wu et al. Sakane et al teaches a neuropeptide and peg alone, readable upon limitation of the closed language "consisting of" as currently amended.

The difference between what is taught by the prior art and that instantly claimed is that while neither Delgado et al, Wu et al, or Sakane et al teach the PEGylation of biphalin, the neuroactive peptide instantly claimed, Wu et al and Sakane et al does teach the pegylation of a neuropeptide that possesses the beneficial properties taught by Delgado et al.

It would have been obvious to one of ordinary skill in the art to PEGylate neuropeptide biphalin as taught by Wu, and Sakane in the pPEGylation of a neuropeptide, BDNF. One would have been motivated to do so given that Wu et al and Sakane et al demonstrated improved pharmacokinetic profiles for the neuropeptide BDNF, and the improved pharmacokinetic profile was in full agreement with the plurality of data presented by Delgado that unrelated peptides that are pegylated have 1) increased plasma half-life, 2) reduced renal clearance, 3) reduced cellular clearance, 4) reduced proteolysis, 5) reduced immunoclearance, 6) reduced immunogenicity and antigenicity, and 7) increased solubility, among 8) other properties of the PEG-protein conjugates. One would have had a reasonable expectation of success in Delgado et al teaches that PEGylating peptides is routine, that such PEGylation provides improved performance in at least eight (8) areas important in pharmacology, and that these improved properties are not protein dependent. Note that Claims 1 and 2 are claims to results that are the effective outcome of PEGylating a protein and would necessarily follow upon pegylation of biphalin.

From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the

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claimed invention, that of pegylating a neuropeptide. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

### Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.**

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thomas S Heard/  
Examiner, Art Unit 1654  
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Primary Examiner, Art Unit 1654